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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,025	12/27/2000	Petrus Johannes Maria Nuijten	99511 US	6121

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FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,025	NUIJTEN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,10,11,19-22,24,29-32,34 and 36-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,10,11,19,20,22,23,29-32 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed July 31, 2006 are acknowledged. Claims 1-6, 8-9, 12-18, 23 and 25-27, 33 and 35 have been cancelled. Claims 7, 19-20, 22, 24, 29, 34 and 36 have been amended. Claims 37-40 have been added.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejection Maintained

3. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims, 22, 24, 28-29 and 31-32 for the reasons set forth on pages 2-9 paragraph 4 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of a *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutical acceptable carrier, wherein the mutated bacterium lacks flagellin does not reasonably provide enablement for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of any *Salmonella* mutated bacterium wherein the mutated bacterium lacks flagellin and wherein the mutated bacterium is attenuated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification has not provided enablement for: A) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritditis, cholerasuis, dublin, abortus-ovi, abortus-equi, derby, habar, heidelberg, agona* and *arizonae* wherein said mutated bacterium lacks flagellin and wherein the vaccine is protective, B) a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritditis, cholerasuis, dublin, abortus-ovi, abortus-equi, derby, habar, heidelberg, agona* and

arizonae, wherein said mutated bacterium lacks flagellin and wherein the mutated bacterium is attenuated.

The claims are drawn to a vaccine composition. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity against *Salmonella* infection or disease induction. The specification teaches that current *Salmonella* vaccines are efficacious however they share a serious disadvantage because they generally induce an antibody population that equals that of an infection with wild-type bacteria because they possess the same antigenic load as the wild-type bacterium. The specification teaches that analysis of antibodies in the serum of *Salmonella*-positive animal does not reveal why the animal is positive, this can be due to vaccination or caused by infection with a virulent strain (page 4). The specification teaches that it would be advantages to have a so-called marker-vaccine comprising an antibody panel that differs from that of the wild-type infection and therefore the host would not make antibodies against the marker (i.e. protein) after vaccination (page 4). The specification teaches that the bacteria is no longer capable of inducing antibodies against at least one antigenic determinant of flagellin or flagella and are considered to be bacteria that do not comprise flagellin or flagella but still possesses all the antigenic determinants (page 6). Example 3 (Experiment 1) of the specification teaches that broilers were inoculated orally, subcutaneously and intramuscularly with a vaccine comprising a wild-type flagellated (fla+) *S. typhimurium* (STMP), a vaccine comprising non-flagellated (fla-) *S. typhimurium (STM2000)* or a vaccine comprising wild-type *S. typhimurium.* The results of this experiment show that 8 out of 10 animals given the wild-type vaccine died and the surviving two had swollen livers with necrotic foci, swollen spleen and pericardial edema. One of the STMP inoculated chickens had a slight swollen liver and one of the STM2000 inoculated chickens had a slightly swollen spleen. No further abnormalities were note in the STMP or the STM2000 inoculated groups. Example 3, (Experiment 2) of the specification teaches a vaccine comprising a wild-type flagellated (fla+) *S. typhimurium* (STMP) and a vaccine comprising non-flagellated (fla-) *S. typhimurium (STM2000)* both administered orally into broilers followed by challenge infection with wild-type *S. typhimurium.* The results of the experiment show that a larger proportion of the chickens in the STMP inoculated group was culture positive after direct plating indicates that this strain colonizes the intestinal tract in higher numbers than the STM2000 strain. Example 4 of the specification teaches that pigs were inoculated orally with STMP or STM2000 followed by an oral challenge infection with wild-type *S. typhimurium.* The results of this experiment in Table 5 show that both vaccine strains were able to reduce fecal shedding of the challenge strain significantly.

The teachings of the prior art regarding *Salmonella* nonflagellated mutants are cited below:

Lockman et al *(Infection and Immunity, January 1990, p. 137-143)* teach nonflagelated mutants of *Salmonella typhimurium* (see the Title). Lockman et al teach that flagella enable bacterial cells to move chemotactically in response to stimuli and there is evidence that these organelles function in the attachment of certain bacteria to solid surfaces (page 141, 1st column). Lockman et al teach that flagella (H antigen) on

the surface of *Salmonella typhimurium* have been characterized as virulence factors that help the bacteria move towards and adhere to the host cells (page 137, 1st column). Lockman et al teach that passive immunization of mice with anti-H antiserum did not protect the animals from a lethal challenge with virulent organisms, although the antiserum inhibited bacterial adherence to intestinal epithelium *in vitro* (page 137, 1st column). Lockman et al teach that nonflagellated strains colonized the intestinal tracts of orally vaccinated mice as well as isogenic flagellated strains yet did not confer equal protection from subsequent lethal challenge by motile *S. typhimurium* (page 137, 2nd column). Lockman et al teach that flagella were necessary for *S. typhimurium* to invade and cause severe disease and the nonflagellated strains were equally proficient at colonization of the murine intestinal tract, but these mutants were deficient in invasion of the reticuloendothelial system (2nd column, page 141). Hackett et al (*The Journal of Infectious Diseases, Vol. 157, January 1988)* teach protective and nonprotective strains of *Salmonella*. Hackett et al teach that when mice were fed strains of *Salmonella* a limited infection in the Peyer's patches was established and generated resistance to subsequent challenge with virulent *S. typhimurium* C5 and the these five strains of *Salmonella* are termed "protective" because they did not give rise to bacteremia or colonization in the liver or spleen (1st column, page 80). Hackett et al teach that also teach eight strains of *Salmonella* and one strain from *E. coli* expressing O-antigens 1,4, 5 and 12 of *S. typhimurium* administered to mice orally that fail to induce resistance to the virulent *S. typhimurium* C5 challenge, these strains are termed "nonprotective" (page 80 in particular, Table 1). Hackett et al teach that *S. typhimurium* C5 and the five protective strains expressed one to two prominent cell envelope polypeptides of 50-55 kDa which were not expressed by the nonprotective strains with the exception of *S. derby*. Hackett et al teach that these polypeptides were loosely associated with the cell envelope and there molecular mass values of about 50 to 55 kDa suggesting that they might be composed of flagellin. Hackett et al confirmed that six of the "protective" strains in which polypeptides were detected contained flagellin either (the H-1i antigen or the H-2 1 antigen) (page 80 and figures 1B and C). Hackett et al teach that *S. typhimurium* C5 and all five of protective strains examined expressed high levels of flagella whereas only one of the eight nonprotective did so (page 81). Hackett et al suggests a correlation between the expression of high levels of flagellin by a *Salmonella* strain, its ability to colonize mice when given orally and its ability to protect against subsequent oral *S. typhimurium* C5 challenge (page 81). Hackett et al determined that there is a correlation between protection and colonization by administering orally to mice flagella-positive (fla+) and flagella-negative (fla-) strains of *Salmonella*. Hackett et al teach that the fla- colonized the Peyer's patch as well as the fla+ strains and when give orally no strain colonized the spleens of infected mice (1st column, page 82). Hackett et al teach that there is a correlation between flagella expression and protective efficacy because mice immunized with fla+ strains showed lower numbers of challenge bacteria in the spleen than did mice immunized with the fla- strains, a result agreeing with the greater protective effects of immunization with the fla+ strains. Hackett et al teach that the levels of challenge strain in the spleens of the immunized mice were similar to three days postinfection, but mice immunized with fla+ strains eliminated the

challenge whereas the mice immunized with fla- strains did not (pages 81-82). Hackett et al teach that it is uncertain whether the relative inefficacy of the fla- vaccines results from their inability to elicit immunity to flagella or from their inability (compared with fla+ strains) to induce immune responses to a wider range of bacterial antigens (2nd column, page 83). Hackett et al teach that flagella promote the intracellular survival of *Salmonella* after ingestion by macrophages and therefore fla+ and fla- bacteria are perhaps "processed" differently by these cells because macrophages can function as antigen presenting cells and this might lead to qualitative and quantitative differences in immune response (2nd column, page 83). Wahdan et al *(Bull World Health Organization, vol. 52, 1975)* teach a nonmotile mutant of *Salmonella typhi* Ty2 which produces high levels of Vi and O titers but is devoid of the flagellar antigen (does not induce formation of H antibody) (page 69). Wahdan et al teach that the nonmotile vaccine was produced with strain TNM1 (page 69). Wahdan et al teach that the TNM1 vaccine is identical to other *S. typhi* whole cell vaccines prepared with Ty2 except that it is devoid of the H antigen and therefore does not interfere with the Widal test for H antibody (page 71). Wahdan et al teach that the TNM1 vaccine did not provide protection. Wahdan et al teach that there is a correlation between the H antibody and protection and suggests that it seems more probable that a property other than the synthesis of flagellar antigen determines immunogenicity and it is absent from the TNM1 non-motile mutant (page 72).

The vaccine composition "is in live attenuated form". The specification teaches that the claimed vaccine compositions can be in a live attenuated form or inactivated (page 11). The specification teaches that the development of live attenuated vaccines in general is difficult and time consuming. The specification teaches that fine-tuning of the degree of attenuation is complex because high virulence causes disease and low virulence induces insufficient protection (page 11). The specification teaches that removal of the flagellin gene does not significantly change the level of attenuation (page 11). Lockman et al *(Infection and Immunity, January 1990, p. 137-143)* teach that the role of the flaF25 mutation in the attenuation of *S. typhimurium* is unclear. The flaF25 mutation was correlated with flagellar biosynthesis and was originally described as a deletion of unknown size within the flaF gene cluster but was subsequently report as a deletion of genes flaFI through flaFV. The flaF25 mutation had been reported to involve not only some of the genes encoding the biosynthesis of flagella but extended into to a previously undescribed virulence gene(s)(2nd column, page 137).

The prior art has taught that flagella (H antigen) enable bacterial cells to move chemotactically in response to stimuli and there is evidence that these organelles function in the attachment of certain bacteria to solid surfaces. The prior art has taught flagella have been characterized as virulence factors. The prior art has taught that fla+ strains express one to two proteins of about 50 to 55 kDa which correspond to the H-1i antigen and the H-2 1 antigen (i.e. flagellin) with the exception of *S. derby*. There is a correlation between high level of flagella, colonization and protection regarding protective *Salmonella* strains. The prior art teaches that although fla+ and fla- strains equally colonize the Peyers patch, the fla+ strains eliminated challenge bacteria whereas the fla- strains did not. The prior art teaches that live oral *Salmonella* vaccines

comprising fla+ strains have been found to be superior against *S. typhimurium* C5 infection in mice. The prior art teaches that fla+ strains may be superior vaccines because macrophages may process bacteria cells that contain flagella differently than those that do not since the prior art has taught that macrophages can function as antigen presenting cells. The prior art has taught that there is a correlation between protection and the H antigen since a nonmotile mutant (lacking the H antigen) of Salmonella typhi did not protect patients against typhoid fever. The prior also teaches that a property other than the synthesis of flagellar antigen determines immunogenicity and it is absent from the TNM1 non-motile mutant. The prior art that the role of attenuation to produce *Salmonella* nonflagelated mutants is unclear.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

In view of the teachings of the specification (or the lack thereof) and the teachings of the prior art there is lack of enablement for the a vaccine comprising any mutated *Salmonella* bacterium from the group consisting of *Salmonella* species *typhimurium, enteritditis, cholerasuis, dublin, abortus-ovi, abortus-equi, derby, habar, heidelberg, agona, arizonae, typhi or paratyphi A and B,* wherein said mutated bacterium lacking flagellin and the said vaccine composition is protective. The specification has shown that the vaccines comprising mutated bacterium lacking flagellin from *S. typhimurium* STMP are protective. It is determine that there are limited working examples commensurate in scope with the instant claims and there is limited guidance provided in the specification as to how to make and use vaccine compositions that comprise a mutation from any *Salmonella* bacterium (other than STM2000) lacking flagellin that are protective against Salmonellosis. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as is broadly claimed because the prior art has taught that many strains of fla- are not protective, do not confer protection from subsequent challenge by motile *Salmonella* bacteria and that mutations such as the flaF25 mutation in the attenuation of *Salmonella* bacterium is unclear.

Applicant's Arguments

A. Applicant urges that the specification is enabled for a vaccine composition comprising an immunological effective amount of a *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutically acceptable carrier. Applicant urges that the cited references fail to show that undue experimentation is necessary to practice the claimed invention.

B. Applicant urges that Lockman et al teach that flagella and motility play a role in the ability of *S. typhimurium* to infect tissue culture monolayers in vitro flagella are not a virulence factor of in vivo murine typhoid. Applicant urges that Hackett et al teach that multiple fla+ strains do not confer protection. Applicant urges that Wahdan et al acknowledges "it seems more probable that a property other than the synthesis of the flagellar antigen determines immunogenicity and is absent form this non-motile motif". Applicant urges that there is nothing in the cited art references to support that the fact the non-flagellated and/or non-motile *Salmonella* were known to maintain virulence and to elicit a protective immune response in vivo.

C. Applicant urges that the specification includes working examples of a non-flagellated mutant *Salmonella* marker vaccine in both chickens and pigs. Applicant urges that Example 4 of the specification shows that the live attenuated flagella-less S. typimurium STM200 vaccine significantly reduced fecal shedding in pigs after a challenge infection with wild-type *S. typhimurium* serotype. This demonstrated the successful immunogenicity of flagella-less S. typhimurim in pigs. Applicant urges that Example 2, shows chickens vaccinated with the *S. enteritidis* fla- were negative for

antibodies to the flagellin protein of *S. enteritidis* thus giving a clearly recognizable marker over those chickens vaccinated with the *S. enteritidis* fla+ vaccine. Applicant urges that the instant specification provides detail instructions for selecting non-motile mutants from serotype *S. typhimurium* SL3261.

D. Applicant urges that all of the methods disclosed in the specification are well known in the art and the level of skill in the art was high at the time of filing the application. Applicant refers to multiple references to support their position (Andersen, 1995, Alberts et al, 1994 and Kutsukake et al).

Examiner's Response to Applicant's Arguments

Applicant's arguments filed July 31, 2006 have been fully considered but they are not persuasive.

A. It is the Examiner's position that the instant specification does not enable all mutated *Salmonella* mutants encompassed by the claimed invention. The instant specification shows a vaccine composition comprising *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutically acceptable carrier. The instant claims do not teach the specific mutants made in the *Salmonella* mutants used in the claimed invention. The instant specification does not indicate what mutations or modifications can be made in the *Salmonella typhimurium* bacterium to arrive at the bacterium used in immunogenic compositions disclosed in the specification. Thus, skilled artisan has not been taught how to make or used the claimed vaccine composition. It appears from the instant specification that Applicant intends to use the immunogenic compositions as

vaccines. It should be noted that the term "vaccine" encompasses the ability of the specific antigen to induce protective immunity against *Salmonella* infection or disease induction. Applicant has not shown that the claimed immunogenic compositions and/or vaccines can be used to protect against *Salmonella* infection.

B. To address Applicant's comments regarding Lockman et al, Lockman et al demonstrate that nonflagellated strains of *S. typhimurium* did not confer equal protection from subsequent lethal challenge by motile *S. typhimurium*. To address Applicant's comments regarding Hackett et al, Hackett et al teach a *S. typhimurium M206* bacterium that did not synthesize flagella (i.e. mutated bacterium lacking flagellin)(page 81) and is not protective against *Salmonella typhimurium* C5 challenge in mice (page 80, table 1). To address Applicant's comments regarding Wahdan et al, Wahdan et al was cited to teach that all *Salmonella* strains which are devoid of the flagellar antigen are not protective.

Therefore, the Examiner disagrees with Applicant's assertion that "none of the cited references support the fact that non-flagellated and/or non-motile *Salmonella* mutants elicit a protective immune response *in vivo*.

C. The Examiner disagrees with Applicant's assertion that "the specification shows working examples that are commensurate with the claimed invention".

It should be noted that claims 22 and 29 are directed improved vaccines and marker vaccine. The instant specification does not enable all mutated *Salmonella enterica* bacterium encompassed by the claimed invention. The specification is only enabled for vaccine compositions for the protection against Salmonellosis comprising

an immunologically effective amount of a *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutical acceptable carrier. To address Applicant's comments regarding Examples 2 and 4, it should be noted that example 2, only shows that chickens were vaccinated with S. enteritidis fla- bacteria and induced antibody production Example 4, merely shows that fecal shedding was reduced in animals receiving the composition comprising live attenuated flagella-less S. typhimurium STM200. It is unclear as to whether reduction in fecal shedding equates to protective immunity.

D. To address the multiple references cited by Applicant to show that all methods in the instant specification are well know in the art and were known at the time of filing the application, it should be noted that the question is not whether the methods were known but whether the instant specification and the state of the art teach or guides the skilled artisan to be able to make the mutated bacterium used in the claimed invention. It should be noted that Kutsukake et al *(Journal of Bacteriology, Feb. 1990, p. 741-747)* teach that in *Salmonella typhimurium*, nearly 50 genes are involved in flagellar formation and function which constitutes at least 13 different operons (see the Abstract). Lockman et al (*Infection and Immunity, January 1990, p. 137-143)* teach that the *Salmonella typhimurium* mutants of the invention were the result of integration of transposon Tn10 into genes responsible for either biosynthesis or the motor activity of these organelles (page 141). Lockman et al teach that mutants of *Salmonella typhimurium* that lack flagella or motility remain virulent in mice (see the Title and the Abstract).

Despite what is disclosed in the specification regarding the synthesis of flagellin and the maturation of flagella, the specification fails to teach how to make or used the mutated *Salmonella* strain of the claimed invention. The cited prior art has taught that *Salmonella* species, for example *S. typhimurium* utilizes over 50 genes in flagellar biosynthesis. The specification has not enabled the skilled artisan to make and use the claimed invention because the specification has not disclosed which genes are modified within nor has the specification taught where within the genes of the biosynthesis pathway modifications are made to arrive at *Salmonella* mutants encompassed by the claimed invention. Therefore, one of skill in the art would require guidance, in order to make or use the claimed invention in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

While, it is known to mutate a bacterium, the location in which the modifications were made to arrive at the *Salmonella* bacterium used in the claimed invention is being questioned.

In view of all of the above the rejection under 35 U.S.C. 112, first paragraph is being maintained.

4. The rejection under 35 U.S.C. 102(b) as anticipated by Joys et al is maintained for claims 7, 11 and 30 for the reasons set forth on pages 10-11, paragraph 5 of the previous Office Action.

The rejection was on the grounds that Joys et al teach compositions comprising fla- (non-flagellate) *Salmonella typhimurium* bacterium in broth culture (page 48-49). Broth culture is a pharmaceutically acceptable carrier because the instant specification teaches that "such a carrier may be as simple as water, but e.g. also comprise culture

fluid in which the bacteria were cultured (page 12). Claim limitations such as "an improved *Salmonella* vaccine" and "an improvement in a marker vaccine" are being viewed as limitations of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The claimed limitation "wherein the marker vaccine is in a freeze-dried or sprayed –dried form is being viewed as a process limitation. Joys et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics of the claimed composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

A. Applicant urges that Joys et al fails to disclose an immunologically effective amount of a live mutated bacteria that are *Salmonella enterica* that in their wild type form carried flagella having at least one antigenic determinant.

B. Applicant urges that the mutants of Joys et al occurred by spontaneous mutation. Applicant urges that freeze-drying the *Salmonella* culture would change the principle operation of the cultures of Joys et al.

C. Applicant urges that claims 22 and 29 has been amended to include an adjuvant and Joys et al does not include an adjuvant. Applicant urges that claims 30-31 are allowable for at least the reason that claim 29 is allowable.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed July 31, 2006 have been fully considered but they are not persuasive.

A. The claims are drawn to an immunogenic composition comprising a live mutated bacterium and a pharmaceutically acceptable carrier wherein the live mutated *Salmonella enterica* in their wild-type form carried flagella having at least one antigenic determinant and wherein after the mutation the live mutated bacteria are not capable of inducing an immune response to at least one antigenic determinant of flagellin.

Joys et al teach live *Salmonella typhimurium* bacterium in broth culture (page 48-49). Broth culture is a pharmaceutically acceptable carrier because the instant specification teaches that "such a carrier may be as simple as water, but e.g. also comprise culture fluid in which the bacteria were cultured (page 12 of instant specification). Joys et al teach that the mutated bacterium are non-flagellated (fla- mutants). Therefore, these mutants are not capable of inducing an immune response to at least one antigenic determinant of flagellin.

B. To address Applicant's comments regarding spontaneous mutation, it should be noted that the there is not particular kind of mutation process recited in the claims. It should remembered that the claims are drawn to a product and the mutation process would be a process limitation. Applicant's comments regarding freeze-drying is also a process limitation in a product claim. It should also be remembered that the products of the prior art reference appear to be the same as the product claimed by the Applicant because they appear to possess the same or similar functional

characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon.

C. Claims 22 and 29 which have been amended to include an adjuvant have been removed from this rejection. Claims 22, 29 and 31-32 have been removed from this rejection. Claims 7, 11 and 30 remain rejected. No claims are allowable.

In view of the all of the above this rejection is maintained.

5. The rejection under 35 U.S.C. 102(b) as anticipated by Lockman et al is maintained for claims 7, 11 and 30 for the reasons set forth on pages 11-13, paragraph 6 of the previous Office Action.

The rejection was on the grounds that Lockman et al teach compositions comprising fla- (non-flagellate, lacks at least one antigenic determinant of flagellin)

Salmonella typhimurium bacterium in broth culture containing glucose (page 139). Broth culture is a pharmaceutically acceptable carrier because the instant specification teaches that "such a carrier may be as simple as water, but e.g. also comprise culture fluid in which the bacteria were cultured (instant specification, page 12). Claim limitations such as "an improved *Salmonella* vaccine" and "an improvement in a marker vaccine" are being viewed as limitations of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The claimed limitation "wherein the marker vaccine is in a freeze-dried or sprayed –dried form is being viewed as a process limitation. Lockman et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics of the claimed composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

A. Applicant urges that Lockman et al fails to disclose an immunologically effective amount of a live mutated bacteria that are *Salmonella enterica* that in their wild type form carried flagella having at least one antigenic determinant. Applicant urges that the mutated bacterium of Lockman et al are not immunogenic because they did not confer immunity. Applicant urges that Lockman et al teach away from an "immunogenic composition".

B. Applicant urges that claims 22 and 29 has been amended to include an adjuvant and Lockman et al does not include an adjuvant.

C. Applicant urges that the mutants of Lockman et al are not inactivated.

Examiner's Response to Applicant's Amendments

A. The claims are drawn to an immunogenic composition comprising a live mutated bacterium and a pharmaceutically acceptable carrier wherein the live mutated *Salmonella enterica* in their wild-type form carried flagella having at least one antigenic determinant and wherein after the mutation the live mutated bacteria are not capable of inducing an immune response to at least one antigenic determinant of flagellin.

Lockman et al teach live *Salmonella typhimurium* bacterium in broth culture containing glucose (page 139). Broth culture is a pharmaceutically acceptable carrier because the instant specification teaches that "such a carrier may be as simple as water, but e.g. also comprise culture fluid in which the bacteria were cultured (page 12 of instant specification). Lockman et al teach that the mutated bacterium are non-flagellated (fla- mutants). Therefore, these mutants are not capable of inducing an immune response to at least one antigenic determinant of flagellin.

To address Applicant's comments regarding Lockman et al teaching away from "immunogenic compositions" because the composition containing the fla- mutants did not confer immunity, it should be remembered that Lockman et al teach that nonflagellated mutants colonized the intestinal tracts of orally vaccinated mice as well as flagellated mutants but yet did not confer equal protection from subsequent lethal challenge (page 137). Thus, Lockman et al does not teach away from immunogenic compositions.

B. Claims 22 and 29 which have been amended to include an adjuvant have been removed from this rejection. Claims 22, 29 and 31-32 have been removed from this rejection. Claims 7, 11 and 30 remain rejected. No claims are allowable.

C. As state above, claim 22 has been removed from this rejection.

In view of the all of the above this rejection is maintained.

6. The rejection under 35 U.S.C. 102(b) as anticipated by Wahdan et al is maintained for claims 7, 11, 19, 22, 24, 28, 29, 30, 32, 34 and newly submitted claims 37-38 for the reasons set forth on pages 13-14, paragraph 7 of the previous Office Action.

The rejection was on the grounds that Wahdan et al teach a vaccine comprising a nonmotile of *Salmonella typhi* Ty2 (TNM1)(see the Abstract and the Title). Wahdan et al teach that the TNM1 was acetone-killed and lyophilized (page 69). Wahdan et al teach that the TNM1 vaccine is identical to other *S. typhi* whole cell vaccines prepared with Ty2 except that it is devoid of the H antigen (lacks at least one antigenic determinant of flagellin) (page 71). Wahdan et al teach that the vaccines were reconstituted the morning of the day it was to be used (page 70). Thus, water is necessarily in the vaccine compositions. Claim limitations such as "an improved *Salmonella* vaccine" and "an improvement in a marker vaccine" are being viewed as limitations of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Wahdan et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics of the claimed composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

Applicant urges that Wahdan et al fails to disclose an immunologically effective amount of an inactivated mutant wherein the inactivated mutant having a mutation in a gene encoding flagellin.

Examiner's Response to Applicant's Arguments

Wahdan et al teach a vaccine comprising a nonmotile *Salmonella typhi* Ty2 (TNM1). Wahdan et al teach a mutant that has a mutation in the gene encoding flagellin because Wahdan et al teach a mutant devoid of the flagellar antigens (see the Abstract). Therefore, these mutants are not capable of inducing an immune response to at least one antigenic determinant of flagellin. It should be noted that the mutants of Wahdan et al were acetone inactivated (3324).

In view of the all of the above this rejection is maintained.

7. The rejection under 35 U.S.C. 102(b) as anticipated by Anderson is maintained for claims 7, 11, 19, 20, 22, 24, 28, 29, 30, 32 and 34 and newly submitted 38 for the reasons set forth on pages 14-15, paragraph 8 of the previous Office Action.

The rejection was on the grounds that Anderson teaches stable non-motile strains of *Salmonella typhi* and *Salmonella paratyphi* (A and B) which are devoid of flagella (lacks at least one antigenic determinant of flagellin) capable of producing the TH, AH or BH antibodies (page 1). Anderson teaches that the *Salmonella* organisms used in the vaccine compositions are heat-killed, alcohol-killed or acetone-killed (page 2). Anderson teaches that the vaccine compositions of the invention can be freeze-dried cultures (page 2). Claim limitations such as "an improved *Salmonella* vaccine" and "an improvement in a marker vaccine" are being viewed as limitations of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the

prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Anderson anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics of the claimed composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

Applicant urges that Anderson fails to disclose an immunologically effective amount of an inactivated mutant wherein the inactivated mutant having a mutation in a gene encoding flagellin.

Examiner's Response to Applicant's Arguments

Anderson teaches a vaccine comprising a nonmotile mutant of *Salmonella typhi* or paratyphi A or B (page 1). Anderson teaches a mutant that has a mutation in the a gene encoding flagellin because Anderson teaches a mutant devoid of the flagellar antigens (page 1). Therefore, these mutants are not capable of inducing an immune response to at least one antigenic determinant of flagellin. It should be noted that the mutants Anderson teaches were inactivated by heat, acetone, phenol or alcohol (page 2).

In view of the all of the above this rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 37 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 37 recites the limitation "...to which the vaccine...". There is insufficient antecedent basis for this limitation in the claim since the claim is drawn to an immunogenic composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 19, 22, 24, 28, 29-30, 32 and 34 are rejected under 35 U.S.C. 103(a) as unpatentable over Anderson *(GB Patent No. 1,109,179, published April 10, 1968, The London Patent Office)* in view of Cox et al *(Vaccine, volume 15, number 3, (1997))*.

Claims 19, 22, 24, 28, 29-30, 32 and 34 are drawn to a improved *Salmonella* vaccine, marker vaccine and immunogenic composition comprising mutated *Salmonella enterica*, pharmaceutically acceptable carrier and an adjuvant, said *Salmonella enterica* lacking at least one antigenic determinant but in mutated form is no longer capable of inducing an immune response to the at least one antigenic determinant of flagellin on a subject to which the vaccine is administered the mutated form having a mutation in a gene encoding flagellin.

Anderson teaches stable non-motile strains of *Salmonella typhi* and *Salmonella paratyphi* (A and B) which are devoid of flagella (lacks at least one antigenic determinant of flagellin) capable of producing the TH, AH or BH antibodies (page 1). Anderson teaches that the *Salmonella* organisms used in the vaccine compositions are heat-killed, alcohol-killed or acetone-killed (page 2). Anderson teaches that the vaccine compositions of the invention can be freeze-dried cultures (page 2).

Anderson teach do not teach the use of adjuvants.

Cox et al teach adjuvants have been used to improve vaccine efficacy since the 1920s (p. 248, 1st paragraph). Cox et al teach that alum is a aluminum salt that has been used in human and veterinary vaccines since 1930 and has an excellent safety record (p. 250, 2nd column, 4th paragraph). Cox et al also teach that cholera toxin is a bacterial toxin and has been proposed as a possible human adjuvant (p. 253, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use adjuvants in the immunological compositions

and vaccine compositions because Cox et al teach that adjuvants have been used to improve vaccine efficacy since the 1920s (p. 248, 1st paragraph).

10. Claims 7, 10, 20, 29, 31-32 and newly submitted claims 37-40 are rejected under 35 U.S.C. 103(a) as unpatentable over Hackett et al (*The Journal of infectious Diseases, Vol. 157, No.1, January 1988)* in view of Cox et al *(Vaccine, volume 15, number 3, (1997)).*

Claims 7, 10, 20, 29, 31-32 and newly submitted claims 37-40 are drawn to a marker vaccine and immunogenic compositions comprising mutated *Salmonella enterica*, pharmaceutically acceptable carrier and an adjuvant, said *Salmonella enterica* lacking at least one antigenic determinant but in mutated form is no longer capable of inducing an immune response to the at least one antigenic determinant of flagellin on a subject to which the vaccine is administered the mutated form having a mutation in a gene encoding flagellin.

Hackett et al teach vaccine composition comprising flagella negative (fla-) strains of live *Salmonella* bacteria (see the Abstract). Hackett et al teach that were constructed by mutating the fla gene (pages 78-79). Hackett et al teach that the vaccine composition were delivered NaCl (page 82).

Hackett et al do not teach the use of adjuvants.

Cox et al teach adjuvants have been used to improve vaccine efficacy since the 1920s (p. 248, 1st paragraph). Cox et al teach that alum is a aluminum salt that has been used in human and veterinary vaccines since 1930 and has an excellent safety

record (p. 250, 2nd column, 4th paragraph). Cox et al also teach that cholera toxin is a bacterial toxin and has been proposed as a possible human adjuvant (p. 253, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use adjuvants in the immunological compositions and vaccine compositions because Cox et al teach that adjuvants have been used to improve vaccine efficacy since the 1920s (p. 248, 1st paragraph).

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Status of Claims

12. Claims 21 and 36 are free of the cited prior art.

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Albert Navarro, can be reached at (571) 272-0861.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
October 14, 2006

NITA MINNIFIELD
PRIMARY EXAMINER